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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,935	08/17/2000	Michael S. Kinch	3220-66874	3254

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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/640,935	Applicant(s) KINCH ET AL.	
	Examiner Misook Yu	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndenc address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6, 10, 12
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election of group II in Paper No. 16 is acknowledged. Because applicant cancelled claims 1-57, the restriction requirement in Paper No. 14 is moot except the species requirement. The originally presented claims in the elected group II were directed to method of cancer treatment, therefore the newly presented claims 58-102 will be examined as they are drawn to cancer treatment using EphA2 agonist and EphA2 agonistic antibody. Original claims 1-57 are cancelled in Paper No. 16 and new claims 58-102 are pending. Claims 58-102 will be examined on merits as they are drawn to method of treating breast cancer as the elected species.

Information Disclosure Statement

This examiner is unable to locate both the list and copy of IDS filed on February 14, 2001, Paper No. 5. When applicant provides replacement of the list and copy, the IDS will be considered without further fee.

Specification

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. The specification does not teach how to make broad ranges of EphA2 agonists that can be used in the method for treatment of metastatic cancer, in the method for reducing the invasiveness of a metastatic cancer cells, or in the method for the proliferative behavior of a metastatic cancer cells except the chimeric ligand, EphrinA1-Fc, which is incorporated by the reference to a publication (Miao et el, see page 3 line 3 of the specification). The specification does not give any guidance how to make EphA2 agonists for accomplishing the purpose in the preambles of the claims, either. Therefore, how to make EphrinA1-Fc is essential to practice the instantly claimed invention and the incorporation of essential material in the specification by reference to a foreign

application or patent, or to a publication is improper. Further, the incorporated reference does not teach how to make the essential material to practice the invention, either. See page 68, Reagents and cells under Methods section of Miao et al (Nature Cell Biology 2, 62-68). Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58-102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. moot

Claims 58-71, and 101 recite "an EphA2 agonist" but it is not clear what the metes and bounds are for the term "an EphA2 agonist". The term " an EphA2 agonist " is not defined by the claims. The specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention for patent protection. The specification at page 3 line 1 says that "agonists to stimulate expression." Does the instantly claimed EphA2 agonist stimulate expression of EphA2 receptor? The specification does not define what expression(s) the EphA2 agonist stimulates. The specification says at page 3 lines 2-8 says that Ephrin A1-Fc, increase the phosphorylation content of EphA2. The specification at page 3, the second paragraph says that "the invention is directed to the use of agonists and antagonists to alter the

expression of EphA2." What kind of altered expression of EphA2 is caused by EphA2 agonist? Does the EphA2 agonist cause overexpression or underexpression of the EphA2 receptor? The specification lists at page 3 lines 11 and 12 several undefined compounds "artificial or hybrid forms of the protein, protein inhibitors, antisense oligonucleotides, or small molecules inhibitors" as possible agonists and antagonists to alter expression of EphA2. However, the specification does not define which one of the compounds listed at page3 lines 11 and 12 is antagonist and which one of the compound is agonist of EphA2. The specification at page 18, Example 8 says that an example of EphA2 agonist, Ephrin A1-Fc, the natural ligand for the receptor linked to heavy chain of immunoglobulin (see Figure 1a of Miao et al, incorporated reference), stimulates tyrosine phosphorylation of EphA2. The On-line Medical Dictionary, Published at the Dept. of Medical Oncology, University of Newcastle upon Tyne Published on 18 Nov. 1997, [retrieved on 2002-07-31] Retrieved from the Internet: <http://www.medical-dictionary.com, defines agonist as "a drug that has affinity for and stimulates physiology activity at cell receptors normally stimulated by naturally occurring substances, thus triggering a biochemical response."

For purpose of the office action, the examiner will assume that an EphA2 agonist claimed in the instant claims is a compound that restore the functions of EphA2 receptor that are lost in the breast cancer cells by increasing the phosphotyrosine contents of the tyrosine kinase receptor. Note Zantek et al (IDS, 1998, Mol Biol. Cell, 9 (suppl): 134a abstract 773; 38th Annual Meeting of the American Society for Cell Biology, December 12-16, 1998).

However, this treatment does not relieve the applicant the burden of responding this rejection.

Claims 72-100, and 102 recite "EphA2 agonistic antibody" but it is not clear what the metes and bounds are for "EphA2 agonistic antibody". The term " an EphA2 agonistic antibody" is not defined by the claims. The specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the claims for patent protection. The term "EphA2 agonistic antibody" is not an art-recognized term. The specification does not

define what is EphA2 agonistic antibody. What does the limitation "agonistic" mean in relationship to an antibody that binds to EphA2 receptor? Does the EphA2 agonistic antibody increases phosphorylation contents of EphA2 or alter expression of EphA2? What is the difference between the antibody recited in the instantly claimed method of claims 72-100, and 102 and an antibody that binds to EphA2 receptor? Is the antibody produced by hybridoma B2D6 an example of EphA2 agonistic antibody?

For purpose of this office action, the examiner will assume that EphA2 agonistic antibody is antibody that restores tyrosine phosphorylation of EphA2 receptor (see page 11 line 5-10 of the specification).

However, this treatment does not relieve the applicant the burden of responding this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, ***had possession*** of the claimed invention.

Claims 58-71, and 101 are drawn to method of metastatic cancer treatment using genus of products claimed as an EphA2 agonist. The specification in Example 8 says that EphrinA1-Fc is an example of EphA2 agonist. EphrinA1-Fc increases the phosphotyrosine content of EphA2. Based on only one product, one cannot predict the types of additional products that might increase the phosphotyrosine contents of EphA2 receptor. Since the genus includes a large number of unpredictable species, possession of only one species is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicant adequately describes EphrinA1-Fc that increases the phosphotyrosine contents of the receptor.

Claims 72-100, and 102 are drawn to method of metastatic cancer treatment using genus of products claimed as EphA2 agonistic antibody. The specification at page 11 lines 5-10 describe the B2D6 treatment of breast cancer cells in culture restored tyrosine phophorylation of EphA2 receptor. Based on only one product, antibody produced by hybridoma B2D6, one cannot predict the types of additional types of EphA2 agonistic antibody that restores phosphotyrosine content of EphA2 receptor.

Claims 58-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to ***enable*** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection involves several different aspects.

Claims 58-65, 72-88, 101, and 102 are drawn to method of breast cancer treatment by administering ***a therapeutically effective amount*** of EphA2 agonist and EphA2 antibodies. The specification discusses prostate tumor treatment using an antibody produced by hybridoma B2D6 in Example 4 (page 12-14). However, the specification fails to teach: 1) if the mice with breast metastic tumor is able to be treated with the antibody; 2) what is ***a therapeutically effective amount*** of B2B6 for breast cancer treatment. The specification does not teach any other EphA2 agonistic antibody for metastatic breast tumor treatment. The specification does not teach method of treatment of metastatic tumor using EphA2 agonist. Without exemplification for accomplishing the purpose stated in preamble of claims 58-65, 72-88, 101, and 102 using the claimed invention in the specification, the lack of sufficient guidance concerning the issue raised above and unpredictability in the art for treating metastatic breast cancer, it is concluded that undue experimentation would be required for one skilled in the art to use the invention as claimed.

Claims 58-65, 68, 71, 72-88, 91, 97, 101, and 102 are drawn to method of cancer treatment using either EphA2 agonist or EphA2 agonistic antibody, claims 66, 67, 89,

90, 92-94 are drawn to method of reducing the invasiveness of a metastatic cancer cells using either EphA2 agonist or EphA2 agonistic antibody, and claims 69, 79, 95, 96, 98-102 are drawn to method for reducing the proliferative behavior of a metastatic cancer cell using either EphA2 agonist or EphA2 agonistic antibody. The claims as written are interpreted as cancer treatment method (with the elected species of breast cancer) using either EphA2 agonist or EphA2 agonistic antibody

The specification discloses: 1) ***in vitro*** data at page 11 lines 5-10 that the antibody produced by hybridoma B2D6 decreased the growth of metastatic breast cancer cells ***in culture***; 2) in Example 3 at page 11-12 that the antibody produced by the hybridoma B2D6 kills metastastic cancer cells ***in culture***. These disclosures suggest that the antibody produced by hybridoma B2D6 could be used as agent to kill metastatic tumor cells ***in culture***. The specification in Example 4 at page 12-14 states that mice challenged with ***prostate primary tumor cells*** to establish metastatic cancer were given with B2D6 (page 14 line 3). The specification further asserts that "B2D6 ***is believed*** to block the primary tumor and metastatic potential of PC3 cells in a dose-dependent manner" (page 14, lines 8 and 9). However, the specification does not teach if B2D6 antibody could be used to treat mice with breast metastatic cancer. The specification at page 18 in Example 8 further discloses that the chimeric ligand for EphA2 receptor, EphrinA1-Fc reduces colony formation of the EphA2 transformed MCF cells in soft agar. However, the specification does not provide any direct data that the antibody produced by B2D6, the chimeric ligand, EphrinA1-Fc, or any other product defined as EphA2 agonist or EphA2 agonistic antibody could be used in treatment of in vivo metastatic breast cancer.

Further, the specification fails to provide enblement for the claims drawn to method of using the EphA2 agonistic antibody because the specification does not teach how to make broad range of EphA2 agonistic antibody that could be used in the claimed invention but discloses only one monoclonal antibody produced by hybridoma B2D6 is able to decrease growth of metastatic breast cancer cells in culture. See Examples1-8 (page8-18). The specification does not teach how to make the specific antibody that is able to decrease growth of metastatic breast cancer cells in culture. It is unclear if the

cell line which produce the antibody having the exact structural and chemical identity of B2D6 is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to the hybridoma cell line producing monoclonal antibody B2D6 it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody used in Example 2 of the instant specification; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. Therefore, it would require undue experimentation to reproduce the claimed antibody species, B2D6 that has the effect in breast cancer cell in culture. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

One cannot extrapolate the teaching of the specification to the claim because it is well known that the art of anticancer ***drug discovery for cancer therapy is highly unpredictable***, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly

possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Further, one cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach that method of in vivo breast cancer treatment. The *in vitro* demonstration of growth inhibition of breast cancer cells with the antibody produced by B2D6 (page 11 lines 5-10) and the in vitro demonstration of EphrinA1-Fc induced reduction of colony formation in soft agar (Example 8 at the last page of the specification) cannot be correlated to the invention as claimed, because the *in vitro* assay either the antibody or the chimeric ligand is in contact with target cells and are not subjected to the defense of the body. In addition, characteristics of cultured cell lines generally differ significantly from the characteristics of in vivo primary cancers or metastatic cancers. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input

of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that either B2D6 or EphrinA1-Fc could kill metastatic malignant breast cells *in vivo*. In addition, anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promotor producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation.

One cannot extrapolate the teaching of the specification to the claims because both EphrinA1-Fc and the B2D6 antibody are proteins and it is well known in

the art that even slight modifications in a peptide or protein structure and can have significant and unpredictable effects on biological activity. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out biological activity and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid (including conservative substitutions) in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or even with conservative glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. The specification does not teach the specific structures responsible for anti-growth activity in culture, nor provide guidance as to what changes in the structure can be made retaining anti-growth activity.

The specification provides insufficient guidance, and provides no working examples of a treatment in vivo which would provide guidance to one skilled in the art to use the claimed invention without undue experimentation, and no evidence has been

provided which would allow one of skill in the art to predict the efficacy of the claimed invention with a reasonable expectation of success. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome the above 112, first paragraph rejections, claims 58-102 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **B2D6** for decreasing the growth of metastatic breast cancer cells in culture and **EphrinA1-Fc** reduces colony formation of the EphA2 transformed MCF cells in soft agar, does not reasonably provide enablement for any other compounds for accomplishing the purpose stated in the preambles of claims 58-102. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 58-65, 68, 71, 72-88, 91, 97, 101, and 102 are drawn to method of cancer treatment using either EphA2 agonist or EphA2 agonistic antibody, claims 66, 67, 89, 90, 92-94 are drawn to method of reducing the invasiveness of a metastatic cancer cells using either EphA2 agonist or EphA2 agonistic antibody, and claims 69, 79, 95, 96, 98-102 are drawn to method for reducing the proliferative behavior of a metastatic cancer cell using either EphA2 agonist or EphA2 agonistic antibody.

The specification discloses: 1) ***in vitro*** data at page 11 lines 5-10 that the antibody produced by hybridoma B2D6 decreased the growth of metastatic breast cancer cells ***in culture***; 2) in Example 3 at page 11-12 that the antibody produced by the hybridoma B2D6 kills metastastic cancer cells ***in culture***. These disclosures suggest that the antibody produced by hybridoma B2D6 could be used as agent to kill metastatic tumor cells ***in culture***. The specification in Example 4 at page 12-14 states that mice challenged with ***prostate primary tumor cells*** to establish metastatic cancer were given with B2D6 (page 14 line 3). The specification further asserts that "B2D6 ***is believed*** to block the primary tumor and metastatic potential of PC3 cells in a dose-

dependent manner" (page 14, lines 8 and 9). However, the specification does not teach if B2D6 antibody could be used to treat mice with breast metastatic cancer. The specification at page 18 in Example 8 further discloses that the chimeric ligand for EphA2 receptor, EphrinA1-Fc reduces colony formation of the EphA2 transformed MCF cells in soft agar. However, the specification does not provide any direct data that the antibody produced by B2D6, the chimeric ligand, EphrinA1-Fc, or any other product defined as EphA2 agonist or EphA2 agonistic antibody could be used in treatment of in vivo metastatic breast cancer.

One cannot extrapolate the teaching of the specification to the claims because the specification contains no working examples of breast cancer treatment in vivo and considering cancer treatment is not trivial matter as discussed above in the paragraph bridging pages 8 and 9, the specification does not provide what structures of either B2D6 or EphrinA1-Fc (see the paragraph bridging pages 11 and 12 of the this office action) is responsible for the antiproliferative activity of B2D6 for the in vitro breast cells or for EphrinA1-Fc being able to reduce colony formation of the cells, and in vitro demonstration could not be directly extrapolated to in vivo application as stated above in the paragraph bridging pages 9 and 10. Considering the limited teachings in the specification, and unpredictability of association of EphA2 agonistic antibody or agonist with breast cancer treatment, it is concluded that undue experimentation would be necessary to practice the full scope of the invention.

Conclusion

No claim is allowed.

As for relevant prior art, Zantek et al (IDS, 1998, Mol Biol. Cell, 9 (suppl): 134a abstract 773; 38th Annual Meeting of the American Society for Cell Biology, December 12-16, 1998) and Zantek et al (IDS, March 1999, Proceedings of the American Association for Cancer Research Annual Meeting, a40: 687 abstract 4537) both teach that proliferation of metastatic cells are inhibited by unidentified compound that activates EphA2 (ECK) receptor.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu, Ph.D.
August 7, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800